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A Comparative Review of Colony-Stimulating Factors

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Summary

The efficacy of dose-intensive chemotherapy in oncology is limited by the duration and severity of neutropenia. Several recombinant DNA factors that alter neutrophil proliferation and function, and are characterised by their ability to stimulate colony formation of myeloid progenitors *in vitro*, have been shown to alter clinical sequelae associated with neutropenia *in vivo*. Two of these factors, granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF), have been approved by the US FDA. One other factor, macrophage colony-stimulating factor (M-CSF), is approved as indicated therapy in Japan. The clinical effects of these agents are compared in this review. Results of clinical trials suggest that the efficacy of G-CSF is greatest when used as an agent to enhance circulation of stem cells and pre–colony-forming progenitor cells. It is also an effective agent in reducing the duration of neutropenia following dose-intensive chemotherapy, thereby leading to a reduction in the incidence of febrile neutropenia. Similar observations were made with GM-CSF, although toxicity with the latter agent appears to be moderately greater than that observed with G-CSF. Functional activity of GM-CSF is broader than that of G-CSF, in that macrophages are affected by GM-CSF. As a result, some

data suggest that GM-CSF may be more applicable to patients with a high risk of infection. There is a suggestion that M-CSF assists neutrophil recovery, although this effect may be indirect, via the induction of other cytokines. The predominant effect of M-CSF appears to be enhancement of macrophage and monocyte function, which may reduce the severity and duration of fungal infection.

Three distinct recombinant human (rh) growth regulatory factors, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and macrophage colony-stimulating factor (M-CSF), which influence functional activity, survival, proliferation and differentiation of myeloid haemopoietic cells, have been identified and molecularly cloned. Each has been approved worldwide for clinical use (to date, M-CSF only in Japan). The activity of G-CSF focuses on proliferation, functional stimulation and differentiation of committed progenitors of neutrophils. GM-CSF has activity similar to that of G-CSF, but is directed towards an earlier progenitor population capable of differentiation towards a monocyte, neutrophil or granulocyte lineage. Both G-CSF and GM-CSF stimulate mobilisation of multipotent progenitors and stem cells from marrow to circulation. The activity of M-CSF focuses on proliferation, functional enhancement and differentiation of monocytes and macrophages.

Preclinical studies indicate improved survival in animal models tested with each cytokine when administered prophylactically before or after cytotoxic chemotherapy. Survival has also been shown to be improved in nonmyelosuppressed animal models given prophylactic G-CSF, M-CSF or GM-CSF before the introduction of bacterial infection and with GM-CSF and M-CSF before the introduction of fungal infection with a variety of *Candida* species. M-CSF has also been shown to improve survival in 1 animal model when administered after the establishment of fungal infection (renal and hepatic abscess).

Evidence from preclinical work suggests not only potential clinical efficacy with use of these cytokines in neutropenia, but also a possible application in patient populations at risk of, or with, active infection. The purpose of this review is to identify established and potential new clinical applications of G-CSF, GM-CSF and M-CSF.

1. Granulocyte Colony-Stimulating Factor

The G-CSF filgrastim is indicated therapy in the US as prophylaxis following myelosuppressive chemotherapy, bone marrow transplant (BMT) and severe chronic neutropenia, and for mobilisation of peripheral blood progenitor cells. Other formulations of G-CSF (i.e. lenograstim) with similar activity are also approved worldwide.

The initial phase III trial investigating G-CSF was done in 210 patients with small-cell lung cancer receiving cyclophosphamide, doxorubicin and etoposide.[1] G-CSF was administered subcutaneously at a dosage of 4 to 8 μg/kg/day from days 4 to 17 after completion of chemotherapy. The duration of neutropenia was markedly shortened in patients receiving the agent during cycle 1 (from 5.6 to 2.4 days) and it was reduced from 3 days to 1 day over all cycles. Additionally, the incidence of febrile neutropenia was reduced (76% in placebo-treated patients, 40% in G-CSF–treated patients). Only 52% of G-CSF–treated patients were hospitalised as opposed to 69% of placebo-treated patients. The incidence of neutropenia was 57% (286 of 500 cycles) in the patients who received G-CSF compared with 77% (416 of 543 cycles) for patients randomised to placebo.

Areas of efficacy as suggested by this trial have been studied in numerous other controlled trials utilising myelosuppressive chemotherapy to treat patients with other solid tumours.[1-30] Reduced duration of neutropenia was consistently observed in patients receiving G-CSF. No evidence of tumour stimulation was seen. Reduction

of febrile neutropenia was commonly observed,[1,2,5-7,10,11,13,18,20,27,29] and a lower rate of documented infection[1,9,15,18] and hospitalisation was recorded in some trials,[1,6,15] but more commonly, the actual clinical benefit in patients receiving G-CSF was either not described or was not observed. Improvement in survival was only rarely observed.[13]

G-CSF was well tolerated in these trials. Toxicity described in the initial phase III trial revealed mild to moderate medullary pain in 24% of patients, which was generally controlled with non-narcotic analgesics.[1] Itching and rashes were also reported to have a higher frequency than in placebo-treated patients. Other studies have described febrile episodes, bone pain and abdominal pain to be more frequent in patients receiving G-CSF in doses above 8 μg/kg/day.[1-30] Rare adverse reactions have included reversible elevations in uric acid, lactic dehydrogenase and alkaline phosphatase, seizures, anaphylactic reactions and transient decreases in blood pressure.

Efforts to utilise G-CSF to escalate myelosuppressive dose levels of cytotoxic chemotherapy have been extensive (see table I).[31-65] Leukopenia continues to be the dose-limiting toxicity of most myelosuppressive regimens evaluated. Higher than expected response rates have been reported, and survival duration is often improved in comparison with previously published survival rates using standard dosage regimens, prompting suggestions of potential benefit obtained from the use of G-CSF and dose-intensive therapy.

Unfortunately, of the 35 trials reviewed in table I, none evaluated dose intensity in phase III trials measuring survival. Therefore, no conclusions can be drawn confirming the efficacy of dose-intensive approaches using prophylactic G-CSF compared with standard chemotherapy or other dose-intensive approaches using prophylactic oral antibiotics to reduce neutropenia-related complications. As a consequence, many practitioners do not consider using G-CSF until after the occurrence of a febrile episode in an early cycle of a multicycle chemotherapy regimen. At this point, the use of G-CSF is recommended to maintain the planned dose intensity.

Maher et al.[66] and Mayordomo and colleagues[67] reviewed the effects of G-CSF, GM-CSF or placebo administered at the time of occurrence of febrile neutropenia. The results of these trials suggested only a limited value in initiating either cytokine after the observation of febrile neutropenia had been made: although neutropenia duration was shortened by 1 day with active treatment, there were no significant differences between active treatments and placebo in both fever duration and percentage of patient deaths after 4 weeks.

1.1 Bone Marrow Transplantation

Several trials have been performed confirming that patients who receive G-CSF achieve an absolute neutrophil count (ANC) of ≥500/mm^3 earlier than controls[68-85] following autologous or allogeneic BMT. Neutrophil recovery to 500 cells/mm^3 is generally 7 days earlier, platelet recovery is not affected, infection is either not affected or is less frequent, and hospital stay is generally not affected or is of shorter duration in G-CSF–treated patients. No adverse effects of G-CSF with graft-versus-host disease (GVHD), rate of relapse, survival, or the occurrence of graft failure or rejection have been observed. A daily subcutaneous route of administration between 5 and 10 μg/kg/day is well tolerated.

1.2 Peripheral Blood Progenitor Cell Transplant

The results of recent trials indicate that sufficient numbers of committed and multipotent progenitor cells can be harvested from the circulation following administration of G-CSF, and reinfused, to enhance neutrophil and platelet recovery after myeloablative or myelosuppressive chemo- or radiotherapy. Data from most trials indicate the need for a 6- or 7-day course of G-CSF. Peak circulation of progenitors occurs on days 4, 5 and 6. Infusion of G-CSF mobilised peripheral blood progenitor cells following dose-intensive (severe

Table I. Use of granulocyte colony-stimulating factor (G-CSF) to alter dose intensity of myelosuppressive regimens

Solid tumour malignancy	Regimen	No. of patients	Effect of G-CSF on dose intensity	Limiting toxicity	Reference
Breast	F, Ep, C	64	MTD Ep = 120 mg/m^2/day	Leucopenia	55
	F, Ep, C	14	F, Ep, C q2wk	Thrombocytopenia	54
	F, Ep, C	32	CEpF q2wk × 6 (93% of patients)	No grade 4	50
	T	25	T = 250 mg/m^2/day (second-line)	Leucopenia	41
	T	52	T = 200 mg/m^2/day (third-line)	Leucopenia	41
	Mi, F	22	MTD Mi = 24 mg/m^2/day	Leucopenia	51
	Ep	50	Ep = 110 mg/m^2 q2wk	Stomatitis	40
	I, Ep	20	I, Ep q2wk	Leucopenia	53
	Ep	42	EP = 110 mg/m^2/day (every 4wk)	Leucopenia	40
	Mi, N	43	MTD Mi = 6 mg/m^2/wk, N = 30 mg/m^2/wk	Leucopenia	56
	I, A	18	MTD I = 2.75g/m^2 × 5 days	Thrombocytopenia	39
	C, A, F	37	MTD C = 4000 mg/m^2, A = 120 mg/m^2	Leucopenia	35
	Mi, M, My	24	MTD Mi = 12 mg/m^2/day	Thrombocytopenia, lethargy	38
	C, Ep, F	30	MTD Ep = 40 mg/m^2/day	Leucopenia	37
Hodgkin's disease	CEAVP	22	MTD C = 1500 mg/m^2/day, E = 160 mg/m^2/day	Leucopenia	36
NHL	CAOP	27	MTD C = 1500 mg/m^2	Leucopenia	64
	COP-BLAM	72	3wk → 2wk schedule	Neutropenia	31
Non–small-cell lung	Cb, E (oral)	39	MTD Cb = AUC 8	Thrombocytopenia	65
	N, Cb	22	MTD Cb AUC 7/4wk, N = 30 mg/m^2/wk	Leucopenia	46
	N, Ep	18	MTD Ep = 90 mg/m^2/day	Leucopenia	52
	Ir, Ci	20	MTD Ir = 80 mg/m^2 on days 1,8,15	Diarrhoea	58
Ovarian	Cb	21	MTD Cb = AUC 9 every 2wk	Thrombocytopenia	44
	T	14	MTD T = 300 mg/m^2/day	Peripheral neuropathy	33
	T	47	T = 250 mg/m^2/day	Leucopenia	42
Ovarian/breast	A	17	MTD A = 375 mg/m^2 over 6wk	Mucositis	32
Small-cell lung	V, Ci	46	MTD VM-26 = 100 mg/m^2/day × 5 days	Thrombocytopenia	48
	T	37	T = 250 mg/m^2/day	Leucopenia	45
	Ci,E – I,A	40	Alternating weeks maintained in 82%	Leucopenia	57
	V, Ci	13	MTD V = 120 mg/m^2 × 3 days	Thrombocytopenia	34
Testicular	BLEOP	13	Reduced treatment delays	Thrombocytopenia	49
Urothelial	M-Vb, A, Ci	35	25% dose increase	Early death	59
Various	T, Ci	32	MTD T = 250 mg/m^2, Ci = 75 mg/m^2	Neurotoxicity	63
	Ir, E	33	MTD Ir = 60 mg/m^2 on days 1-3, E = 60 mg/m^2 on days 1-3	Diarrhoea	62
	T (3 hr)	35	MTD T = 300 mg/m^2	Peripheral neuropathy	47
	T, To	46	MTD T = 230 mg/m^2/day	Neuromuscular	43
	Ci, To	38	MTD C = 75 mg/m^2/day, To = 1 mg/m^2/day × 5 days	Leucopenia	60
	Pi	38	MTD Pi = 185 mg/m^2	Leucopenia	61

Abbreviations: A = doxorubicin (adriamycin); AUC = area under the concentration-time curve; BL = bleomycin; C = cyclophosphamide; Cb = carboplatin; Ci = cisplatin; E = etoposide; Ep = epirubicin; F = fluorouracil; I = ifosfamide; Ir = irinotecan; M = methotrexate; Mi = mitoxantrone; MTD = maximum tolerated dose; My = mitomycin; N = vinorelbine; NHL = non-Hodgkin's lymphoma; O = vincristine; q2wk = every 2 weeks; P = prednisone; Pi = prioxantrone; T = paclitaxel; To = topotecan; V = teniposide (VM-26); Vb = vinblastine.

myelosuppressive) chemo- or radiotherapy, leading to a decrease in the number of days required for neutrophil and platelet recovery, and reductions in hospital stay.[86-104] Results of G-CSF–mobilised peripheral blood stem (progenitor) cell (PBSC) infusion following myeloablative chemotherapy are

summarised in table II.[105-120] These results suggest that neutrophil and platelet recovery is more rapid in patients who receive PBSC mobilised with G-CSF compared with those who received BMT, regardless of whether G-CSF was administered after BMT.

A reduction in the number of episodes of febrile neutropenia, the number of platelet transfusions and duration of hospital stay has been observed in some studies.[105,107,108,112,116,120] The optimal dosage of G-CSF for mobilisation is 10 μg/kg/day, administered as a single daily subcutaneous injection. G-CSF can also be administered for mobilisation following modest cytotoxic chemotherapy. Enhanced concentration of circulating progenitor cells is observed; however, it remains unclear if the added toxicity related to the cytotoxic agent used for mobilisation improves clinical outcome. Long term engraftment has been found to be stable in patients who have received peripheral blood progenitor cells. The use of allogeneic PBSCs mobilised by G-CSF is in early investigation, but results suggest more rapid neutrophil and platelet recovery compared with allogeneic marrow infusion and no effect on acute GVHD, although chronic GVHD may be increased.[121-125]

1.3 Chronic Neutropenia

Patients with idiopathic chronic neutropenia or congenital neutropenia experience increased morbidity and mortality as a result of recurrent infection related to the neutropenic state. Administration of G-CSF significantly increases and sustains a higher neutrophil level, resulting in less infection and hospital time.

In one trial[126] involving 123 patients (median age 12 years) with severe chronic neutropenia (ANC <500/mm^3), G-CSF was administered daily to 1 group of patients by subcutaneous injection with dose adjustments to maintain an ANC of >1500/mm^3; another group received no therapy for 4 months. After 4 months, a crossover of patients who did not receive G-CSF was allowed. All patients ended up receiving G-CSF. 108 patients achieved a median ANC of ≥1500/mm^3 while receiving G-CSF.

The incidence and duration of infection was reduced 50%, the incidence of oral pharyngeal ulcers was reduced from 26 to 0%, and antibiotic use was reduced from 49 to 20% while patients were receiving G-CSF. 28 hospitalisations occurred in patients receiving G-CSF compared with 44 in patients not receiving the drug over the same period. The median ANC was 210/mm^3 in patients who did not receive G-CSF, and it was maintained above 1500/mm^3 in patients who did. Patients with congenital neutropenia appeared to require higher dosages of G-CSF (2.2 to 4 μg/kg/day) than patients with idiopathic or cyclic neutropenia (0.5 μg/kg/day) in order to achieve an ANC of ≥1500/mm^3. Mild to moderate bone pain was reported in 30 to 40% of patients and was controlled with non-narcotic analgesics. Splenomegaly developed in 30% of patients after treatment with G-CSF; 6% developed thrombocytopenia (platelet count <50 000/mm^3). This appeared to correlate with the onset of splenomegaly. Myelodysplasia or leukaemia developed in 3% of patients, and 12% who had normal cytogenetic studies at baseline were found to have abnormalities 18 to 52 months after initiation of G-CSF.

Since acute leukaemia and myelodysplastic syndrome may occasionally be preceded by a state of severe neutropenia, it is difficult to determine if this rare occurrence of leukaemia is related to G-CSF or is part of the natural history of disease.[127-129] Results of other phase I/II trials have also been consistent with results observed in this trial;[127,128] therefore, since quality of life is improved,[130] G-CSF is recommended for prophylactic use in patients with severe chronic neutropenia (ANC <500/mm^3).

1.4 Leukaemia and Leukaemia-Related Syndromes

G-CSF stimulates the proliferation of myeloid leukaemia blasts[131] *in vitro*, leading to concerns with clinical use in acute leukaemia. However, controlled trials have failed to supply any evidence

Table II. Results of granulocyte colony-stimulating factor (G-CSF)–mobilised peripheral blood stem (progenitor) cell infusion (PBSC) following myeloablative chemotherapy

Solid tumour malignancy	Mobilising regimen	No. of patients	Day when ANC > 500/mm^3		Day when platelet count > 50 000/mm^3		Duration of hospital stay (days)		Cytokine postinfusion		Reference
			BMT	PBSC	BMT	PBSC	BMT	PBSC	BMT	PBSC	
Breast	F, Ep, C/G-CSF	29		9					–	+	109
Breast, non-Hodgkin's lymphoma	G-CSF	15[a]	19	13		35	27	18	+	+	105
	IL-3 → G-CSF	23[a]	19	12		25	27	19	+	+	105
Hodgkin's disease, non-Hodgkin's lymphoma	Chemo/G-CSF	10		15					–	–	114
Multiple myeloma	C, P/G-CSF	37		12					–	+	110
Neuroblastoma (paediatric)	C, E/G-CSF	5		18					–	–	115
	G-CSF	6		14					–	–	115
Non-Hodgkin's lymphoma	G-CSF	26		10					–	+	118
	G-CSF	27[b]	14	11			23	17	+	+	116
	CA, Mi/G-CSF	30		13					–	–	117
	G-CSF	39		10					–	+	118
	CA, Mi/G-CSF	20		12		16.5		21	–	–	119
	CA, Mi/G-CSF	20		10		14.5		21	–	+	119
	G-CSF	29		10		15		13	–	+	111
Non-Hodgkin's lymphoma, breast	G-CSF	49[a]	19	10			39	29	–	+	112
Various	CA, E/G-CSF	42[a]		13			29	19	–	–	120
	C/G-CSF	42		14		13		16	–	+	113
	G-CSF	12		13					–	–	106
	G-CSF	14[a]	10	9	39	15	17	14	+	+	107
	G-CSF	34[a]	21	15	31	18	31	22	+	+	108

a Historical BMT controls (the prospective patients received the cytokine).

b Prospective BMT controls.

Abbreviations: A = Doxorubicin (adriamycin); ANC = absolute neutrophil count; BMT = bone marrow transplant; C = cyclophosphamide; CA = cytarabine; Chemo = chemotherapy; E = etoposide; Ep = epirubicin; F = fluorouracil; IL = interleukin; Mi = mitoxantrone; P = prednisone.; – = cytokine not administered ; + = cytokine administered.

that G-CSF adversely affects the time of leukaemia relapse, response rate, duration of response or survival.[132-140] Neutrophil recovery has occurred at an earlier rate in patients receiving G-CSF following induction or consolidation chemotherapy. Platelet recovery and infection have not been affected, although duration of hospital stay was reduced in only 1 trial[135] despite improvements in ANC in all trials, except one in which ANC was not reported.[138]

In one trial,[141] G-CSF was administered to neutropenic leukaemia patients at the onset of documented sepsis in one group of patients (n = 16 episodes), and comparison was made with patients being treated in the same manner, but without G-CSF. There was no statistical difference in mortality related to sepsis between these groups.

G-CSF has also been administered to patients with refractory anaemia and myelodysplastic syndrome.[142-147] It was well tolerated and neutrophil levels increased without adverse effects on blast cells. Platelet counts were not affected. To date, no trials have been published looking at the effect of the prophylactic use of G-CSF on infection in myelodysplastic syndrome.

One trial comparing G-CSF with placebo found shorter survival in patients with refractory anaemia and excess blasts, although it is unclear if the survival difference was related to G-CSF or prognostic characteristics between the two groups.[146] Recently, it was observed that patients with myelodysplastic syndrome who received the combination of G-CSF and erythropoietin had a greater elevation of haemoglobin levels than when erythropoietin alone was given.[147]

G-CSF has also been given in combination with antithymocyte globulin (ATG) and cyclosporin to aplastic anaemia patients with severe neutropenia ($<500/mm^3$).[145] In one trial involving 40 patients, it was well tolerated; 33 patients responded to ATG with trilineage engraftment and became transfusion-independent a median of 115 days after initiation of treatment.

2. Granulocyte-Macrophage Colony-Stimulating Factor

In the US, GM-CSF derived from yeast is indicated as therapy in neutropenic patients after autologous or allogeneic BMT, and for mobilisation of autologous peripheral blood progenitor cells. *Escherichia coli*–derived GM-CSF is also approved in Europe for prophylactic treatment following dose-intensive chemotherapy.

The recommended dose of GM-CSF is 250 $\mu g/m^2$/day administered daily as a 2- or 4-hour intravenous infusion, although activation and tolerability using the same dosage and schedule, but administered subcutaneously, is not different. GM-CSF administration is contraindicated in patients with excessive myeloid leukaemia blasts (>10%) in the bone marrow or peripheral blood, and during concomitant administration with radiotherapy or chemotherapy.

The toxicity attributed to this agent in healthy volunteers includes low-grade fevers, abdominal/bone pain, fluid retention, headaches and transient rashes in 10 to 30% of patients. These toxicities are difficult to identify in prospective, controlled trials involving dose-intensive chemotherapy, since they also occur as a natural consequence of the treatment regimen.

2.1 Myelosuppressive Chemotherapy

GM-CSF has similar activity to G-CSF in the treatment of patients receiving myelosuppressive chemotherapy, but toxicity (low grade fevers, myalgias, bone pains, abdominal pains) is considered slightly greater. The US FDA has not approved the use of GM-CSF for solid tumour patients receiving myelosuppressive chemotherapy. Results of trials with GM-CSF in patients receiving myelosuppressive chemotherapy reported a reduction in neutropenia,[148-153] while reported reductions in infection and hospital stay were reported additionally in some studies.[152,153] Further work exploring the use of this agent with dose-intense regimens is ongoing.

2.2 Autologous Bone Marrow Transplant

The primary trial in autologous BMT which led to approval of GM-CSF in the US was a multicentre trial involving patients with non-Hodgkin's lymphoma and acute lymphocytic leukaemia.[154] In this trial, time to achieve an ANC of >500/mm^3 was 6 days shorter (18 *vs* 24 days) and that taken to reach a figure of ≥1000/mm^3 was 8 days shorter (24 *vs* 32 days), and the duration of hospitalisation was 10 days less (21 *vs* 31 days) in patients receiving GM-CSF, compared with placebo recipients. Duration of infection and duration of antibacterial therapy were also significantly shorter in GM-CSF–treated patients. Additional trials have confirmed the results of the initial phase III study with rhGM-CSF.[154-165] The incidence and type of adverse effects in patients receiving either GM-CSF or placebo were not statistically significantly different.

In one retrospective analysis, infectious complications in 106 consecutive historical patients who underwent autologous BMT for lymphoid malignancy were compared with those in 50 consecutive, similarly treated patients who received prophylactic GM-CSF (Nemunaitis J, et al., unpublished data). 40% of control patients developed documented infection compared with only 13% of the GM-CSF–treated patients. It was suggested that there was a benefit from GM-CSF during the period of severe neutropenia before differences in neutrophil levels between the study groups were detectable, suggesting evidence to support the use of GM-CSF for its functional effects.

2.3 Marrow Graft Failure

Nearly 1% of HLA-matched sibling allogeneic donor transplant patients, 5% of unrelated donor transplant patients, and 10 to 15% of mismatched allogeneic transplant patients will have delayed neutrophil recovery resulting from immunological rejection of donor cells.[166] Graft failure without evidence of immunological rejection can also occur. Potential causes of nonimmunological graft failure include low stem cell inoculum, post-transplant infection (i.e. cytomegalovirus) or drug toxicity. With the exception of patients with aplastic anaemia, fewer than 20% of patients not treated with GM-CSF will survive 5 years.[167,168]

For the purpose of evaluating the use of GM-CSF in the setting of marrow graft failure, a uniform definition of graft failure was adopted in one large trial.[167] Patients who did not achieve a neutrophil level of >100/mm^3 by day 28 after transplant, those who did not achieve a neutrophil count of 100/mm^3 by day 21 after transplant with evidence of infection, and those who initially achieved an ANC of >500/mm^3 for at least 1 week and who subsequently dropped to <500/mm^3 for at least 1 week, were defined as having graft failure. Historical patients who fulfil this definition have a 2-year survival of less than 20%.[167]

The predominant cause of death of patients with graft failure is infection. In an initial trial, GM-CSF was administered at a dose of 250 μg/m^2/day by 2-hour intravenous infusion for 14 days. If the neutrophil count did not reach >500/mm^3 within 3 weeks of therapy, a second, and possibly a third, course of GM-CSF was administered.[167,169]

The drug was well tolerated in an initial phase I/II trial[167] and was, therefore, explored in a more extended study involving 185 patients.[169] The median survival of patients undergoing allogeneic BMT who received GM-CSF was 97 days, compared with 35 days in a historical matched control group.[160,170] In the case of autologous BMT, the figure was 474 days, against 161 days in a historical matched control group. Multivariate analysis of possible factors that may affect survival in patients receiving GM-CSF failed to identify patients more likely or less likely to respond. Improvement in survival and reduction of infection-related mortality was also observed in other trials exploring the use of GM-CSF in patients with marrow graft failure.[171,172]

2.4 Allogeneic Bone Marrow Transplant

Given the evidence of efficacy with GM-CSF in autologous transplant, and lack of toxicity in both autologous and allogeneic transplant patients with

graft failure, phase I/II trials in patients undergoing matched sibling and unrelated donor transplant were performed (see table III).[173-184] The results revealed earlier neutrophil recovery, occasional improvement in infection rates and shorter duration of hospitalisation. No adverse effects on GVHD or survival were observed. Phase III trials with GM-CSF in allogeneic transplant recipients confirmed the efficacy of the drug.

In the FDA-approval trial, the time to achieve a neutrophil level of 500/mm^3 in GM-CSF–treated patients was 4 days shorter than that with placebo (13 *vs* 17), the time to achieve an ANC of ≥1000/mm^3 was 5 days shorter (14 *vs* 19), the number of patients with infection was fewer (30 *vs* 42), the number of patients with bacteraemia was smaller (9 *vs* 19), and fewer days were spent in hospital (24 *vs* 25). Interestingly, the incidence of severe mucositis (grade III/IV) was also significantly improved in the GM-CSF group (4 of 53 *vs* 16 of 56) compared with placebo in this trial; however, mucositis has not been shown to be affected in other trials. The severity or duration of GVHD, relapse rates and survival were not different between GM-CSF– and placebo-treated patients. Patients undergoing unrelated bone marrow transplant also showed earlier neutrophil recovery, but no other factors such as infection, hospital duration or mucositis were improved.[175]

2.5 Peripheral Blood Stem Cell Transplant

The minimum number of mononuclear cells required for consistent engraftment rates is between

Table III. Granulocyte-macrophage colony-stimulating factor (GM-CSF) in allogeneic bone marrow transplant

Reference	Cytokine	Type of BMT	No. of patients	GVHD prophylaxis	Day when ANC > 500/mm^2	Day when patient platelet-independent	Percentage of GVHD ≥ grade III[a]	Survival (y) [%]
Dewitte et al.[173]	Placebo	Matched sibling	28	T cell depletion	20	NR	6	2 [40]
	GM-CSF	Matched sibling	29	T cell depletion	15	NR	3	2 [58]
Powels et al.[174]	Placebo	Matched sibling	20	CSP	16	NR	15	1 [20]
	GM-CSF	Matched sibling	20	CSP	13	NR	5	1 [42]
Anasetti et al.[175]	Placebo	Unrelated	63	CSP/MTX	22	NR	NR	1 [51]
	GM-CSF	Unrelated	61	CSP/MTX	20	NR	NR	1 [39]
Nemunaitis et al.[176]	Placebo	Matched sibling	56	CSP/P	17	24	12	1 [63]
	GM-CSF	Matched sibling	53	CSP/P	13	20	15	1 [55]
Hiraoka et al.[177]	Placebo	Matched sibling	16	CSP/MTX	22	NR	NR	1 [56]
	GM-CSF	Matched sibling	16	CSP/MTX	14	NR	NR	1 [48]
Nemunaitis et al.[178]	Historical controls	Matched sibling	50	CSP/P	19	21	ND	
	GM-CSF	Matched sibling	28	CSP/P	14	23	14	
Nemunaitis et al.[179,180]	Historical controls	Matched sibling	43	CSP/MTX	24	20	ND	
	GM-CSF	Matched sibling	19	CSP/MTX	20	23	6	
	Historical controls	Unrelated	78	CSP/MTX	23	31	ND	2 [49]
	GM-CSF	Unrelated	103	CSP/MTX	21	23	25	2 [57]
Naparstek et al.[181]	Historical controls	Matched sibling	40	CSP/MTX	18	23	ND	
	GM-CSF	Matched sibling	20	CSP/MTX	14	16	ND	
Nemunaitis et al.[182]	GM-CSF	Unrelated	9	CSP/P	16	NR	50	
Chap et al.[183]	GM-CSF	Matched sibling	2	CSP/P	13	NR	50	
Nemunaitis et al.[184]	GM-CSF	Matched sibling	6	CSP/P	12	14	0	

a Grade III or IV GVHD indicates tat the condition is 'very severe'.

Abbreviations: ANC = absolute neutrophil count; BMT = bone marrow transplant; CSP = cyclosporin; GVHD = graft-versus-host-disease; MTX = methotrexate; ND = not different from comparator group (specific percentages not reported); NR = not reported; P = prednisone.

Table IV. Morbidity related to mobilisation with cyclophosphamide at dosages shown

	Kotasek et al.[186]		To et al.[189]		Jagannath et al.[187]		Boiron et al.[188]		Rosenfeld et al.[190]		Sureda et al.[195]	
	7 g/m^2	4 g/m^2	7 g/m^2	4 g/m^2	6 g/m^2	6 g/m^2 + GM-CSF	7 g/m^2	7 g/m^2 + GM-CSF	4 g/m^2	4 g/m^2 + GM-CSF	4 g/m^2	4 g/m^2 + GM-CSF
No. of cycles	23	52	23	37	36	39	21	10	10	10	12	15
Day when ANC <1000/<500/mm^3	10/NR	7/NR	NR/NR	NR/NR	NR/18	NR/15	NR/20	NR/14	15/NR	12/NR	NR/10	NR/7
Day when platelet count <50 000/mm^3	7	1	NR	NR	18	15	15	13	NR	NR	NR	NR
Percentage of patients with febrile neutropenia	100	21	100	44	57[a]	57[a]	NR	NR	50	0	92	73
Percentage of sepsis	39	10	NR	NR	23[a]	23[a]	5	20	NR	NR	42	26
Duration of hospital stay (days)	NR	NR	NR	NR	NR	NR	23	22	NR	NR	NR	NR

a 57% of patients developed febrile neutropenia and 23% documented infections in both groups. GM-CSF was described as not making a difference in infection morbidity but data were not shown.

Abbreviations: ANC = absolute neutrophil count; GM-CSF = granulocyte-macrophage colony-stimulating factor; NR = not reported.

3×10^8 and 6×10^8 cells/kg.[185] Primitive and committed progenitor cells express CD34 antigen. Levels of harvested CD34 surface antigen expressive cells have been shown to be predictive of the rate of neutrophil and/or platelet recovery after peripheral blood stem cell transplant (PBSCT). A minimum of 2×10^6 CD34+ cells/kg are necessary to achieve rapid, consistent and sustained engraftment.[185]

Administration of cyclophosphamide (at a variety of doses ranging from 4 to 7 g/m^2), the combination of GM-CSF with cyclophosphamide, and the administration of a variety of chemotherapy agents with or without GM-CSF, are other methods which have been shown to be effective strategies for mobilisation of progenitor cells. Each of the methods described has certain advantages and disadvantages.

Mobilisation with cyclophosphamide, when that drug is combined with rhGM-CSF, induces a greater volume of circulating progenitor cells than mobilisation by cytokines alone. However, the toxicity related to cyclophosphamide may be significant[186-191] (see table IV). Morbidity related to the duration of pancytopenia, febrile neutropenia and infection has been associated with substantial hospitalisation and occasional mortality. In one trial, patients were kept in the hospital for 23 days after the administration of cyclophosphamide for mobilisation.[189] In this trial, the addition of rhGM-CSF did not appear to reduce morbidity, despite an improvement in neutrophil recovery.

An advantage to mobilising PBSC with chemotherapy is that most patients requiring mobilisation often have progressive disease and may not be able to wait 1 to 2 weeks for mobilisation with cytokines alone before receiving antitumour agents. There is no significant evidence that tumour cells are mobilised into circulation during recovery after chemotherapy alone, after chemotherapy combined with growth factors or after growth factors alone. Contaminating tumour cells are less frequently identified in mobilised peripheral blood than in bone marrow.[192-195] The rate of neutrophil recovery and the frequency of clinical complica-

Table V. Cytokine-mobilised peripheral blood stem-cell transplant versus historical bone marrow transplant, with and without cytokines[204]

	Arm[a]			Historical placebo	Historical GM-CSF
	1	2	3		
Mononuclear cell count/kg/apheresis	2.5	1.3	1.3		
Day when absolute neutrophil count					
>100/mm^3	12	16	11	14	13
>500/mm^3	14	24	13	26	19
>1000/mm^3	16	23	15	33	26
Day when platelet count > 20 000/mm^3	15	28	10	29	26
Duration of hospital stay (days)	19	27	18	33	27

a Arm 1 = rhIL-3 5 μg/kg/day prior to rhG-CSF 5 μg/kg/day; arm 2 = rhIL-3 5 μg/kg/day prior to rhGM-CSF 5 μg/kg/day; arm 3 = rhIL-3 5 μg/kg/day combined with rhG-CSF 5 μg/kg/day.

Abbreviation: rhIL-3 = recombinant human interleukin-3.

tions following infusion of GM-CSF–mobilised PBSCs are similar to those obtained with G-CSF.[187,190,196-202]

Over the past 2 years, methods of mobilising PBSCs have changed. Few centres now mobilise PBSCs following chemotherapy without cytokines. Most centres harvest the cells after mobilisation with chemotherapy combined with cytokines, or after cytokines alone. Nonrandomised studies performed in similar patient populations, receiving similar preparative regimens, reveal a reduction in duration of neutropenia and duration of hospital stay in patients receiving cytokines after marrow transplant, and further improvement in patients receiving PBSCT.[203]

Studies directly comparing PBSCT against autologous BMT in similar patient populations suggest that there is a marked advantage to the use of PBSCs after myeloablative regimens over BMT with or without prophylactic cytokines, particularly with respect to platelet recovery.[190,191] Rapid neutrophil and platelet recovery is important for maintenance of a dose-intensive chemotherapy regimen, and may reduce the cost of intensive therapy. Overall, despite the lack of completed randomised trials, data suggest that the use of stem cells and progenitor cells contained in peripheral blood substantially reduces morbidity compared with the results achieved with bone marrow transplant.

Other cytokines are also being explored to potentiate the effects of GM-CSF or G-CSF for mobilisation. Table V compares engraftment rates in patients receiving IL-3/G-CSF– and IL-3/GM-CSF–mobilised cells with those in historical BMT patients who received no cytokines or GM-CSF after marrow infusion.[204] Engraftment rates in patients receiving cytokine-mobilised PBSCs and in historical BMT recipients in table V are consistent with other published data.

2.6 Disorders in Marrow Function

Several phase II studies show increases in neutrophil levels in patients with aplastic anaemia and myelodysplastic syndrome who receive GM-CSF, although in patients with more severe aplastic anaemia (ANC <100/mm^3) neutrophil stimulation is not as significant. Stimulation of non-neutrophil lineages and infection is not affected.[205-208] Patients with other states of chronic neutropenia have also been investigated using GM-CSF (i.e. chronic idiopathic neutropenia, congenital neutropenia, sickle-cell–related neutropenia, autoimmune neutropenia). Neutrophil recovery was improved in most patients; however, no other clinical benefit or positive effect on survival was evident.[206]

2.7 Leukaemia

Several large placebo-controlled trials have been performed with GM-CSF in leukaemia patients following induction chemotherapy. Neutrophil recovery was earlier in patients receiving GM-CSF. In one trial involving acute myelogenous

leukaemia, GM-CSF recipients'[209] time to achieve a neutrophil level of >500/mm^3 was 4 days shorter, and the incidence of infection was less (52 *vs* 75%) than in patients who received placebo. Achievement of a complete response was 69% in the GM-CSF–treated patients compared with 55% in the placebo-treated patients, although subsequent relapse occurred more frequently in the former (33 *vs* 14%) within the first 100 days after induction therapy. Overall survival duration was 378 days for patients receiving GM-CSF compared with 260 days in those receiving placebo. Other trials have reported similar effects on neutrophil recovery, but have not shown a survival advantage in patients who received GM-CSF.[209-213]

3. Macrophage Colony-Stimulating Factor in Fungal Infections

M-CSF is a glycoprotein that stimulates survival, proliferation, and differentiation of mononuclear phagocytes.[214] It also primes macrophages to enhance production of oxygen reduction products when stimulated by micro-organisms. As a result, M-CSF–treated monocytes have increased capability for intracellular killing of fungal and bacterial micro-organisms.[215-219]

In order to evaluate its clinical potential and antimicrobial activities, M-CSF was administered to neutropenic and infected mice.[215,220-224] Survival was significantly improved in mice infected with bacterial and fungal organisms compared with the results obtained from placebo, suggesting that M-CSF directly enhanced host resistance to infection by functionally activating monocytes.

The initial trial with M-CSF in patients with fungal infection was a phase I dose-escalation trial in which rhM-CSF was administered concomitantly with amphotericin B to 24 BMT patients with invasive fungal infection.[225] Patients who received ≥2000 μg/m^2/day of M-CSF had a temporary reduction in platelet count by 61 000/mm^3 from baseline while receiving the drug. GVHD in patients who had received allografts was not affected. Neutrophil, monocyte and lymphocyte counts were not altered.

Six patients had complete histological and radiological resolution of fungal infection during the study period. 12 patients were not evaluable for response (primarily because of refusal, or medical unsuitability, to undergo diagnostic surgical procedures for histological confirmation of infection resolution) and 6 patients did not respond to rhM-CSF. Two of the 6 patients who did not respond received less than 7 days of therapy, and 1 patient had an ANC of 0 and was unable to tolerate granulocyte transfusions. Ten of the 24 patients (42%) survived 100 days after initiation of therapy. No patients (10 with myeloid malignancy) developed recurrent disease while receiving M-CSF.

After completion of the phase I trial, 22 additional patients were treated with M-CSF at a dose of 2000 μg/m^2/day.[226,227] The results for all 46 M-CSF–treated patients were compared with those for 58 similar historical control patients (table VI). Patients with a Karnofsky score of >20% who received M-CSF and who had invasive *Candida* infection had better survival than historical controls.

Highly purified (not recombinant) M-CSF is indicated as therapy in Japan to accelerate granulo-

Table VI. Survival (percentage of total) of patients who received recombinant human macrophage colony-stimulating factor (rhM-CSF) compared with historical controls[226]

Group	>20% Karnofsky performance score		≤20% Karnofsky performance score		Total
	Candida	*Aspergillus*	*Candida*	*Aspergillus*	
rhM-CSF	50 (n = 20)[a]	20 (n = 10)	0 (n = 11)	0 (n = 5)	**27 (n = 46)**
Controls	15 (n = 33)[a]	0 (n = 5)	9 (n = 11)	0 (n = 9)	**5 (n = 58)**
p-Value[b]	0.004	0.675	0.565	0.228	**0.027**

a Includes 1 patient with mucor who did not survive as a result of progressive infection.

b Mantel Cox analysis.

cyte recovery following allogeneic transplant, dose-intensive therapy of ovarian cancer and induction therapy of AML. In allogeneic transplant recipients, M-CSF was administered to 51 patients and the results were compared with concurrent nonrandomised controls. Two patients developed fever in association with the M-CSF infusion; otherwise there was no toxicity. The incidence and severity of GVHD, the rate of graft failure and the rate of recurrent disease and survival were not altered. Patients who received M-CSF for 14 daily doses achieved ANCs of 500 and 1000/mm^3 4 ($p < 0.05$) and 8 days earlier,[228-230] respectively, than control patients. M-CSF is administered as a short intravenous infusion at a dose of 8×10^6 IU/dose.

Ohno et al.[231] recently completed a randomised, placebo-controlled trial in patients with AML. M-CSF (n = 88) or placebo (n = 94) were administered at a dose of 8×10^6IU by 2-hour intravenous infusion for 14 days following consolidation chemotherapy. Patients receiving M-CSF completed all 3 chemotherapy courses a median of 17 days earlier than placebo-treated patients, as a result of more rapid neutrophil and platelet recovery. The duration of febrile neutropenia was also reduced in M-CSF–treated patients, from 10.4 to 6.4 days.

4. Conclusions

Both G-CSF and GM-CSF have established roles in minimising neutropenia-related complications following cytotoxic chemotherapy. The use of these cytokines, particularly G-CSF, has revolutionised the field of dose-intensive chemotherapy for the practising oncologist by permitting outpatient management of dose-intensive approaches through reduction of febrile neutropenic episodes and enhanced platelet recovery following infusion of cytokine-mobilised peripheral blood progenitor cells.

The results of this review suggest that G-CSF is the predominant cytokine utilised in oncology to reduce neutropenia-related complications associated with myelosuppressive chemotherapy. G-CSF is not as effective once neutropenia occurs, and it does not appear to be effective in the setting of active infection when patients have normal or low neutrophil levels.

The field of transplantation has been dramatically altered with the use of peripheral blood progenitor cell infusions as a source of stem cells following aggressive myeloablative therapy. Based on a slightly improved tolerability assessment, G-CSF is also the cytokine of choice for mobilisation.

Data suggest that GM-CSF would be appropriately used in the setting of severe myelosuppression (possibly when the expected neutrophil level would be below 500 cells/mm^3 for ≥7 days following dose-intensive chemotherapy). Patients appear to be at greater risk of infection during episodes of prolonged neutropenia, and the macrophage-stimulating effects of GM-CSF appear to reduce infection-related complications. GM-CSF is also an effective mobilisation agent, although modest bone pain and low-grade fever associated with GM-CSF make it a slightly more difficult cytokine to tolerate than G-CSF in this setting.

A benefit of either of these cytokines in the setting of infection without associated neutropenia has not been confirmed, although there is preliminary evidence of some efficacy.

Data suggest that M-CSF would be the most likely agent to be effective in the setting of fungal infection, whereas GM-CSF may be more appropriate in bacterial infection; however, these results are only preliminary and cannot be recommended for routine use.

Future trials will probably involve expansion of trials involving dose-intensive approaches with G-CSF. Future utilisation of GM-CSF will, most likely, involve situations of high infection risk. M-CSF, despite marked activity in enhancing monocyte and macrophage function, is not undergoing further investigation in the US.

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Erratum

Vol. 54, No. 2, page 234: The address for correspondence and reprints should have read: Dr Tsuneharu Baba, Vice-Director, Dohtai Clinic Kajiwara, 2-34-1 Kajiwara, *Kamakura 247*, Japan.